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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

PLOUËT et al.

Atty. Ref.: 1487-28

Serial No. 10/566,679

Group: unknown

Filed: February 1, 2006

Examiner: Unknown

For: NOVEL ANTI-ANGIOGENIC AGENT AND ITS USE, IN PARTICULAR WITHIN THE
FRAMEWORK OF THE TREATMENT OF CANCER

* * * * *

September 28, 2006

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1540

Sir:

SUBMISSION

Submitted herewith is a copy of the English translation of the International
Preliminary Examination Report issued in the corresponding PCT/FR2004/002050.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

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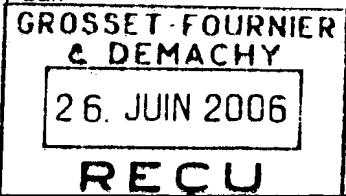
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NOTIFICATION DE TRANSMISSION DE COPIES
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PRÉLIMINAIRE INTERNATIONAL
SUR LA BREVETABILITÉ (CHAPITRE I OU CHAPITRE II
DU TRAITE DE COOPERATION EN MATIERE DE BREVETS)

(règles 44bis.3.c) et 72.2 du PCT)

Destinataire :

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FRANCE



Date d'expédition (jour/mois/année) 22 juin 2006 (22.06.2006)	NOTIFICATION IMPORTANTE
Référence du dossier du déposant ou du mandataire WOB03CNRGIOG	
Demande internationale n° PCT/FR2004/002050	Date du dépôt international (jour/mois/année) 30 juillet 2004 (30.07.2004)
Déposant CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE etc	

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Il est rappelé au déposant que, lorsqu'une traduction de la demande internationale doit être remise à un office élu, cette traduction doit comporter la traduction de toute annexe du rapport préliminaire international sur la brevetabilité (chapitre II).

Il appartient au déposant d'établir la traduction en question et de la remettre directement à chaque office élu intéressé dans le délai applicable (règle 74.1). Voir le volume II du Guide du déposant du PCT pour de plus amples renseignements.

Bureau international de l'OMPI
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TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS

PCT

RAPPORT PRÉLIMINAIRE INTERNATIONAL SUR LA BREVETABILITÉ

(chapitre I du Traité de coopération en matière de brevets)

(règle 44bis du PCT)

Référence du dossier du déposant ou du mandataire WOB03CNRGIOG	POUR SUITE À DONNER		Voir le point 4 ci-dessous
Demande internationale no. PCT/FR2004/002050	Date du dépôt international (<i>jour/mois/année</i>) 30 July 2004 (30.07.2004)	Date de priorité (<i>jour/mois/année</i>) 01 August 2003 (01.08.2003)	
Classification internationale des brevets (8 ^e édition, sauf indication d'une édition antérieure) Voir les informations pertinentes dans le formulaire PCT/ISA/237			
Déposant CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE			

<ol style="list-style-type: none"> 1. Le présent rapport préliminaire international sur la brevetabilité (chapitre I) est établi par le Bureau international au nom de l'administration chargée de la recherche internationale selon la règle 44bis.1.a). 2. Ce RAPPORT comprend un total de 8 feuilles, y compris la présente feuille de couverture. <p style="margin-top: 10px;">Dans les feuilles jointes, toute référence à l'opinion écrite de l'administration chargée de la recherche internationale doit être entendue, à la place, comme une référence au rapport préliminaire international sur la brevetabilité (chapitre I).</p>																								
<ol style="list-style-type: none"> 3. Le présent rapport contient des indications relatives aux points suivants : <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 15%;"><input checked="" type="checkbox"/></td> <td style="width: 15%;">Cadre n° I</td> <td style="width: 70%;">Base de l'opinion</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Cadre n° II</td> <td>Priorité</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Cadre n° III</td> <td>Absence de formulation d'opinion quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Cadre n° IV</td> <td>Absence d'unité de l'invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Cadre n° V</td> <td>Déclaration motivée selon l'article 35.2) quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle; citations et explications à l'appui de cette déclaration</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Cadre n° VI</td> <td>Certains documents cités</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Cadre n° VII</td> <td>Certaines irrégularités relevées dans la demande internationale</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Cadre n° VIII</td> <td>Certaines observations relatives à la demande internationale</td> </tr> </table> 4. Le Bureau international communiquera le présent rapport aux offices désignés conformément aux règles 44bis.3.c) et 93bis.1 mais pas avant l'expiration du délai de 30 mois à compter de la date de priorité (règle 44bis.2), sauf si le déposant a présenté une requête expressément à cet égard en vertu de l'article 23.2). 	<input checked="" type="checkbox"/>	Cadre n° I	Base de l'opinion	<input checked="" type="checkbox"/>	Cadre n° II	Priorité	<input type="checkbox"/>	Cadre n° III	Absence de formulation d'opinion quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle	<input type="checkbox"/>	Cadre n° IV	Absence d'unité de l'invention	<input checked="" type="checkbox"/>	Cadre n° V	Déclaration motivée selon l'article 35.2) quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle; citations et explications à l'appui de cette déclaration	<input checked="" type="checkbox"/>	Cadre n° VI	Certains documents cités	<input type="checkbox"/>	Cadre n° VII	Certaines irrégularités relevées dans la demande internationale	<input type="checkbox"/>	Cadre n° VIII	Certaines observations relatives à la demande internationale
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<input type="checkbox"/>	Cadre n° VIII	Certaines observations relatives à la demande internationale																						

<p style="text-align: right;">Bureau international de l'OMPI 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>no de télécopieur +41 22 740 14 35</p>	<p>Date d'établissement du présent rapport 12 June 2006 (12.06.2006)</p> <p>Fonctionnaire autorisé Athina Nickitas-Etienne</p> <p>no de téléphone : +41 22 338 89 95</p>
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see Form PCT/ISA/220

PCT

Translation

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

		Date of mailing (day/month/year)
Applicant's or agent's file reference see Form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/FR2004/002050	International filing date (day/month/year) 30.07.2004	Priority date (day/month/year) 01.08.2003
International Patent Classification (IPC) or both national classification and IPC A61K38/18, A61P35/00, A61P17/00, A61P19/02, A61P27/02, A61P37/06		
Applicant CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE		

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP European Patent Office-Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901-0	Authorized officer
Facsimile No. +49 30 25901-840	Telephone No. +49 30 25901-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material
 in written format
 in computer readable form
 - c. time of filing/furnishing
 contained in the international application as filed.
 filed together with the international application in computer readable form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Reference is made to the following documents:

D1: Perbal et al., 1999. PNAS, 96(3): 869-874.
D2: Iruela-Arispe et al., 1999. Circulation, 100: 1423-1431
D3: Inoke et al., 2001. FASEB J., 16(2): 219-221.

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INTERNATIONAL SEARCHING AUTHORITY

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Box No. II Priority

1. The following document has not yet been furnished:

copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
 translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Since a copy of the prior application has not been supplied the opinion on novelty, inventive step and possibility of industrial applicability has been established on the presumption that the date of the claimed priority is valid.

However, the patent application published on 21 January 2004 (EP1382347) has not been considered as relevant prior art.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. V <u>Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</u>																									
<p>1. Statement</p> <table> <tr> <td align="center">Novelty (N)</td> <td>Claims</td> <td>1 - 9</td> <td align="center">YES</td> </tr> <tr> <td></td> <td>Claims</td> <td>_____</td> <td align="center">NO</td> </tr> <tr> <td align="center">Inventive step (IS)</td> <td>Claims</td> <td>_____</td> <td align="center">YES</td> </tr> <tr> <td></td> <td>Claims</td> <td>1 - 9</td> <td align="center">NO</td> </tr> <tr> <td align="center">Industrial applicability (IA)</td> <td>Claims</td> <td>1 - 9</td> <td align="center">YES</td> </tr> <tr> <td></td> <td>Claims</td> <td>_____</td> <td align="center">NO</td> </tr> </table>		Novelty (N)	Claims	1 - 9	YES		Claims	_____	NO	Inventive step (IS)	Claims	_____	YES		Claims	1 - 9	NO	Industrial applicability (IA)	Claims	1 - 9	YES		Claims	_____	NO
Novelty (N)	Claims	1 - 9	YES																						
	Claims	_____	NO																						
Inventive step (IS)	Claims	_____	YES																						
	Claims	1 - 9	NO																						
Industrial applicability (IA)	Claims	1 - 9	YES																						
	Claims	_____	NO																						
<p>2. Citations and explanations:</p> <p>I. Document D1, which is considered to be the closest prior art to the subject matter of claims 1, 5 and 6, describes (see abstract; page 869, right column, last paragraph - page 870, left column, 2nd paragraph) the Nov human gene (NOVH) and its domains (see figure 1). NOVH is 100% identical to SEQ ID NO: 2 of the present invention. Furthermore, its C-terminal domain is capable of binding to fibulin 1C, which would indicate that NOVH has a role in the adhesive mechanisms of cells.</p> <p>As a result, the subject matter of claims 1, 5 and 6 differs from this known document D1 in that the present patent application results from demonstrating the angiogenesis inhibiting activity of NOV.</p> <p>II. The subject matter of claims 1, 5 and 6 is therefore novel (PCT Article 33(2)).</p> <p>Claims 2-4 and 7-9, which are dependent on claims 1, 5 and 6, therefore also satisfy as such the conditions stipulated by the PCT regarding novelty.</p>																									

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2004/002050

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Inventive step

I. The present application does not meet the conditions set out in PCT Article 33(1) because the subject matter of claims 1, 5 and 6 does not involve an inventive step as defined in PCT Article 33(3).

D1 (see above) describes the NOVH protein with its domains and in the discussion suggests that NOVH has the role of negative regulator, as well as the proteins ELM1 and RCOP-1 (see page 873, right column, 3rd paragraph) and encourages the identification of proteins capable of interacting with NOVH so as to understand the biochemical characteristics of this protein (see page 874, left column, last paragraph).

Moreover, D2 discusses the inhibition of angiogenesis by thrombospondin (TSP-1), describes the sequences responsible for the angiostatic effect of TSP-1 (see figures 4 and 5), and identifies two independent paths via which TSP-1 can block the angiogenic signals of FGF-2 and VEGF in the endothelial cells (see abstract; page 1424, right column, 3rd paragraph - page 1429, left column, 2nd paragraph).

D3 discloses the inhibition of angiogenesis by CTGF. CTGF binds to VEGF and the TSP-1 domain is responsible for the angiogenesis inhibiting effect. The interaction between CTGF and VEGF prevents the attachment of VEGF to the endothelial cells. The angiogenesis inhibiting activity due to CTGF has been demonstrated *in vitro* in an analysis of the formation of endothelial cells and *in vivo* in the

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INTERNATIONAL SEARCHING AUTHORITY

International application No.

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

Matrigel injection model in mice (see page 125, 3rd paragraph - page 127, 3rd paragraph).

Taking into account the above points, combining all the features mentioned in claims 1, 5 and 6, in view of the technical teachings of documents D1, D2 and D3, represents a normal technical approach for a person skilled in the art. A person skilled in the art would have been prompted to find out whether the NOVH protein, which belongs to the same family as CTGF and possesses a TSP-1 domain, also binds to VEGF and inhibits the angiogenesis inhibiting activity of VEGF.

The subject matter of claims 1, 5 and 6 therefore does not involve any inventive step (PCT Article 33(3)).

II. The dependent claims 2-4 and 7-9 do not contain any feature which, in combination with those of any one of the claims to which they refer, defines a subject matter which meets the requirements of the PCT regarding inventive step, see documents D1-D3 and the corresponding passages cited in the search report.

III. It should be pointed out that the angiogenesis inhibiting activity is located in the C-Ter part on aa 188 to 357 (SEQ ID NO: 12, this sequence contains the domain of the thrombospondin type (SEQ ID NO: 8) and the C-terminal domain rich in cysteines (SEQ ID NO: 10)), and that the N-ter fragment (corresponds to a sequence comprising aa 1-187 of NOV) does not exhibit any inhibiting activity.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. PCT/FR2004/002050

Box No. VI	Certain documents cited			
1. Certain published documents (Rule 43bis.1 and 70.10)				
Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)	
EP1382347	21.01.2004	17.07.2002	17.07.2002	
2. Non-written disclosures (Rule 43bis.1 and 70.9)				
Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)		

See form 210